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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,297	08/24/2005	Joseph Alexander Lasky	ON/4-32744A	1063

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	**PAPER NUMBER**
1628	

MAIL DATE	DELIVERY MODE
08/12/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/532,297	**Applicant(s)** LASKY, JOSEPH ALEXANDER	
	Examiner TIMOTHY P. THOMAS	**Art Unit** 1628	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 August 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *05 August 2010*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *2,5,7,11 and 12*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Timothy P Thomas/
Examiner, Art Unit 1628

Continuation of 11. does NOT place the application in condition for allowance because: The rejections of record are maintained for the reasons of record:

Claims 12, 2, 5, 7 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pulmonary hypertension in the sense of the meaning of reduction of pulmonary hypertension in individuals with pulmonary hypertension, does not reasonably provide enablement for treating individuals in the sense of the meaning of prophylactic treatment.

It is noted that the addition of new claim 12 to this rejection is necessitated by the claim amendment adding this new claim.

The record indicates that curative treatment with the traditional meaning of completely getting rid of the ailment; i.e., when curative is construed to have the more usual meaning in the art of completely alleviating pulmonary hypertension, that this definition of curative treatment as a result of the method step is not enabled. Simply reducing levels of pulmonary hypertension is not identical to the complete removal of pulmonary hypertension (which would be required by the usual definition of "cure"). This meaning of "curative" is still applicable to the disclosed meaning of "efficacy in treating ongoing episodes of pulmonary hypertension"; the application to this disclosed definition indicates the intended outcome of curative therapy would be the complete alleviation of all episodes of pulmonary hypertension as the result. This result is not considered enabled based on the similarity of this outcome to prevention, and the basis established on the record with respect to prevention and this meaning of curative treatment.

Applicant argues that since the amended claim clearly does not include prophylactic treatment, the stated basis for the rejection is overcome. This is presuasive with respect to the prophylactic treatment embodiment, but not with respect to curative treatment, where the meaning of curative is the complete alleviation of pulmonary hypertension episodes (with no recurrance of pulmonary hypertension). The reasons established on the record are also applicable to this meaning of curative treatment, when construed in the broadest reasonable meaning.

Applicant further states that the scope of claim 12 is not different from previously pending claim 10 because claim 10 required the patient to be suffering from pulmonary hypertension. It is not clear how this is relevant to the rejection basis.

Claims 12, 2, 5, 7 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goncharova, et al. ("PI3K is required for proliferation and migration of human pulmonary vascular smooth muscle cells"; 2002 Mar 8; Am. J. Physiol. Lung Cell. Mol. Physiol.; 283: L354-L363; cited in a prior Office Action); Tanabe, et al. ("Mechanical stretch augments PDGF receptor β expression and protein tyrosine phosphorylation in pulmonary artery tissue and smooth muscle cells"; 2000; Molecular and Cellular Biochemistry; 215: 103-113; cited in a prior Office Action); Zimmermann, et al. (WO 99/03854 A1; 1999; IDS 4/21/2005 reference AM); and Dingli, et al. ("Unexplained Pulmonary Hypertension in Chronic Myeloproliferative Disorders"; 2001; Chest; 120 (3): 801-808; cited in a prior Office Action).

It is noted that the addition of new claim 12 to this rejection is necessitated by the claim amendment adding this new claim.

Applicant argues based on previously filed arguments that the cited references do no more than suggest a connection between PDGFR and pulmonary hypertension and that a best provide a suggestion to experiment with PDGFR inhibition for the treatment of pumonary hypertension. All previously presented arguments have been previously addressed in Office Actions. It is not agreed that the references in combination only provide a "suggestion to experiment"; at least three different rationales are of record porviding motivation for carrying out the recited step of the instant claims, leading to a reasonable expectation of reduction of pulmonary hypertension. The record indicates, in part: blocking PI3K-dependent human PVSM cell motility is expected from inhibition of PDGF; and reduction of PDGF levels would be expected to benefit in therapy of pulmonary hypertension, based on these references. Taking into account that Zimmerman clearly indicates imatinib and imatinib mesylate are active inhibitors of PDGF, and are useful in diseases where vascular smooth-muscle cell migration and proliferation where PDGR and PDGF-R play a role (see 4/1/2008 Office Action, Item 7, pp. 7), the administration of the claimed compounds would have been expected to provide a benefit in therapy of pulmonary hypertension. There would have been a reasonable expectation of success based on the teachings of these references, taken in combination.

This is not the same facts as KSR Rationale (E) "Obvious to Try"; instead it is a rationale more consistent with KSR Rationale (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention (see MPEP 2141).

Applicant argues case law from Bayer v. Barr, 575 F.3d 1341; 91 USPQ2D 1569 *Fed. Cir. 2009) is applicable, which focuses on the limitations of the obvious to try rationale. Since the rationale is closer aligned to KSR rationale (G), the arguments that this decision is applicable to this case is not persuasive.

Applicant argues that the general unpredictability of the general approach is clear from the Examiner's position in the 112, 1st paragraph rejection; that none of the cited references contains disclosure that would lead to the skilled artisan to reasonably predict that all compounds known to inhibit PDGFR would have utility for treating pulmonary hypertension. It is important to differentiate between the bases for the enablement rejection and the expectation based on the references in combination. The enablement rejection is based on the absolute cure embodiment within the scope of the claims. If in fact, such a cure were supported by data, the model data should have demonstrated no pulmonary hypertension occuring in the animals receiving the dosage of the claimed compound. If fact, this did not occur. An increase in pulmonary hypertension is reported in the specification for the animals receiving imatinib, subjected to the hypobaric-hypoxic conditions. The fact that this occurs is inconsistent with enabling curative treatment when cure has the meaning discussed above.

In contrast, the expectation based on the references in combination is to reduce the level of vascular remodeling. There is a reasonable expectation for a benefit for therapy in pulmonary hypertension based on the rationales: 1) both Goncharova and Tanabe implicate the role of PDGF-R in pulmonary hypertension and Zimmerman teaches imatinib is useful in diseases where PDGF-R plays a role; 2) Gocharova teaches cell proliferation and motility is a critical step in vascular remodeling, imatinib inhibits such processes; and 3) Tanabe teaches phosphorylation of PDGF receptor β by stretch in endothelial cells is a component of pulmonary hypertension, such phorsphorylation is inhibited by imatinib; as well as the supporting observation of the correlation between pulmonary hypertension and chronic myeloproliferative disorders, for which imatinib therapy is commonly used, taught by Dingli. These reasons, taken as a whole would have provided motivation for administering imatinib to a patient with pulmonary hypertension.

Applicant further argues that the combined disclosure of references would not have lead the skilled artisan to select imatinib from the potential PDGFR inhibitors. This is not persuasive. The record indicates: taking into account that Zimmerman clearly indicates

imatinib and imatinib mesylate are active inhibitors of PDGF, and are useful in diseases where vascular smooth-muscle cell migration and proliferation where PDGR and PDGF-R play a role (see 4/1/2008 Office Action, Item 7, pp. 7), the administration of the claimed compounds would have been expected to provide a benefit in therapy of pulmonary hypertension. This provides motivation to adminster imatinib.